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APPLICATION NUMBER	FILING DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO.
08/259,321	06/10/94	REZAIE	A OMRF106CIP

EXAMINER

HM12/0331

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ART UNIT	PAPER NUMBER
1642	26

DATE MAILED: 03/31/99

This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

OFFICE ACTION SUMMARY

☒ Responsive to communication(s) filed on 11/11/99

☒ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 D.C. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire 3 month(s), ~~or thirty days,~~ whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) 1-3, 5, 7-8, 14-15, 17-21 is/are pending in the application.
Of the above, claim(s) _____ is/are withdrawn from consideration.
☐ Claim(s) _____ is/are allowed.
☒ Claim(s) 1-3, 5, 7-8, 14-15, 17-21 is/are rejected.
☐ Claim(s) _____ is/are objected to.
☐ Claim(s) _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.
☐ The drawing(s) filed on _____ is/are objected to by the Examiner.
☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.
☐ The specification is objected to by the Examiner.
☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.
☐ received in Application No. (Series Code/Serial Number) _____.
☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☐ Notice of Reference Cited, PTO-892
☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____
☐ Interview Summary, PTO-413
☐ Notice of Draftperson's Patent Drawing Review, PTO-948
☐ Notice of Informal Patent Application, PTO-152

--SEE OFFICE ACTION ON THE FOLLOWING PAGES--

★ U.S. GPO: 1996-421-632/40206

1. Claim 3 has been amended.

Claims 1-3, 5, 7-8, 14-15 and 17-21 are pending.

2. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

3. Claim 3 is objected to because of the following informalities: Newly amended claim 3 is grammatically incorrect in the recitation "humanized. biological fluid." The format of claim 3 is also in improper, as the claim contains two periods. Appropriate correction is required.

4. The objection of claims 2 and 15 as not complying with the Sequence Rules and Regulations is maintained. Both claims recite two unique amino acid sequences (the third and fourth sequences of the Markush Group) that are not set forth in the "Sequence Listing." The applicant states that these two amino acid sequences are a portion of longer amino acid sequences (SEQ ID NO:10 and SEQ ID NO:12) included in the current Sequence Listing. The applicant argues that "the requirement is that the sequence must be present in a Sequence Listing in computer readable form; not that each portion described or claimed be present in a separate Sequence Listing. To do so would result in unnecessary duplication and paperwork for all parties. Each of the claimed sequences present in claims 2 and 15 are described in a Sequence Listing." This is not found persuasive. Each of the four amino acid sequences recited in claims 2 and 15 is a distinct sequence, even though two of the sequences are nested within the other two. Thus, each of the four amino acid sequences requires its own, separate listing in the Sequence Listing. Again, the applicant is advised to either amend the claims to refer to these two amino acid sequences in text only, "amino acids 20-139 of SEQ ID NO:10 and amino acids 23-129 of SEQ ID NO:12," deleting the recitations of the actual amino acid sequences. Alternatively, the applicant can provide a replacement Sequence Listing that includes the listing of these two amino acid sequences.

5. As currently drafted, this application contains two amino acid sequence disclosures (in claims 2 and 15, see above paragraph) that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 C.F.R. § 1.821(a)(1) and (a)(2). However, as these two amino acid sequences are not included electronic and paper sequence listings, this application fails to comply with the requirements of 37 C.F.R. §§ 1.821-1.825. APPLICANT IS GIVEN THE RESPONSE PERIOD OF THIS OFFICE ACTION WITHIN WHICH TO COMPLY WITH THE SEQUENCE RULES, 37 C.R.F. §§ 1.821-1.825. Failure to comply with these requirements will result in ABANDONMENT of the application under 37 C.F.R. § 1.821(g). Extensions of time may be obtained by filing a petition accompanied by the extension fee under the provisions of 37 C.F.R. § 1.136. In no case may an applicant extend the period for response beyond the six month statutory period. Please note that if claims 2 and 15 are amended according to the first recommendation in the above paragraph 5, this notice of failure to comply with the sequence rules becomes moot.

6. The rejection of claims 1-3, 5, 7-8, 14-15 and 17-21 under 35 U.S.C. 112, second paragraph, as being indefinite, is withdrawn in view of the amendment to claim 3.

7. As the parent application, 7/982,832 does not provide support for "humanized antibodies" or the synthesis of antibodies in insect cells, for the application of the art, priority to the instant filing date only (06/10/94) is extended to claims drawn to humanized antibodies and antibodies synthesized in insect cells.

8. The rejection of claims 1-3, 5, 7-8, 14-15 and 17-21 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-3 of U.S. Patent No. 5,202,253 in view of Morrison or Queen is maintained. Please see the arguments below.

9. The rejection of claims 1-3, 5, 7-8, 1415 and 17-21 under 35 U.S.C. § 103 as being unpatentable over any of U.S. Patent No. 5,202,253 (the '253 patent), U.S. Patent No.

5,147,638 (the '638 patent), D'Angelo or Stearns in view of view of Morrison, Queen (WO 90/07861) or Queen (U.S. Patent 5,530, 101, 6/25/96, filed 12/19/90) is maintained.

The teachings and motivations provided by the cited references have been covered at length in previous office actions. Briefly, each of U.S. Patent No. 5,202,253, U.S. Patent No. 5,147,638, D'Angelo and Stearns teach monoclonal antibody HPC4 and the hybridoma cell line that secretes the HPC-4 antibody. These references do not teach the humanization of said antibody or its synthesis in bacterial or insect cells. However, Morrison and the two Queen references teach the complete methodology for the cloning and sequencing cDNA from the hybridoma cell line that secretes a given murine monoclonal antibody the nucleotide sequences that encode the immunoglobulin heavy and light chains (For example, see Example 5 of the Queen '101 patent) and complete methodologies for the construction of a humanized antibody using the hypervariable sequences obtained from these nucleotide sequences.

It would have been prima facie obvious to one of ordinary skill in the art at the time the claimed invention was made to apply the basic methodology taught by Queen in order to clone the genes encoding the HPC-4 monoclonal antibody from the hybridoma cell line ATCC No. HB 9892 taught by U.S. Patent No. 5,202,253 or U.S. Patent No. 5,147,638, D'Angelo and Stearns. In doing so one of ordinary skill in the art would have obtained antibodies having the structural characteristics of those claimed. One of ordinary skill in the art would have been motivated to produce recombinant antibodies having the variable region of HPC-4 in order to obtain the advantages discussed by Morrison, for example, on page 1207. One would have been motivated to produce chimeric antibodies or humanized antibodies comprising human antibody sequences in view of the art-recognized advantages of reduced immunogenicity in human hosts obtained by replacing rodent antibody sequences with human sequences as discussed by Morrison and Queen.

The applicant makes reference to "enclosed copies of the seven Declarations under 37 C.F.R. 1.132 filed during the prosecution of these applications" demonstrating that "the claimed murine antibody was totally unique and that was why it was patentable. Moreover, it was impossible to predict that one could obtain another antibody with the same kind of reactivity." Copies of the Declarations referred to were not be found in the instant application for

consideration by the examiner. The applicant is invited to submit copies of these Declarations with the next communication to the office. However, it is noted that the evidence referred to, demonstrations that the murine HPC4 monoclonal antibody (secreted by hybridoma cell line ATCC No. HB 9892) is "totally unique" and that one of skill in the art can not obtain additional antibodies with the same specificity as HPC4 would not be found persuasive against the instant rejection. The instant claims are all limited to antibodies with the binding specificity of "the monoclonal antibody produced by the hybridoma deposited with the American Type Culture Collection as ATCC No. HB 9892" (the murine HPC4 monoclonal antibody). The cited patents are fully enabling for the the monoclonal antibody produced by the hybridoma deposited with the American Type Culture Collection as ATCC No. HB 9892. Thus, to make and use the claimed invention, one of skill in the art does not need to produce additional antibodies with specificities the same as that produced by the hybridoma deposited with the American Type Culture Collection as ATCC No. HB 9892.

The applicant argues the '638 and '253 patents, the D'Angelo and Stearns references (which teach the hybridoma cell line that produces the HPC-4 murine monoclonal antibody but do not teach methods for the humanization of antibodies) and the Queen and Morrison references (which teach methods for the humanization of antibodies but does not teach the HPC-4 antibody) separately, do not enable the claimed invention. This is not found persuasive. As stated in the previous office actions, it is the combined teachings of these references that teaches and enables the humanization of the HPC-4 monoclonal antibody.

The applicant argues that the Stearns reference was overcome as prior art in the prosecution of the parent applications and thus is not eligible as art in the prosecution of the instant application. In the absence of the presentation of the previous arguments and evidence presented in these parent applications for consideration in the instant rejection, this argument is not found persuasive. Affidavits or declarations, such as those under 37 CAR 1.131 and 37 CAR 1.132, filed during prosecution of the parent application do not automatically become a part of this application. Where it is desired to rely on an earlier filed affidavit or declaration, the applicant should make the remarks of record in the later application and include a copy of the

original affidavit or declaration filed in the parent application. The applicant is invited to submit such arguments or evidence for consideration by the examiner.

The applicant argues the '638 and '253 patents and the D'Angelo and Stearns references do not "enable" the HPC-4 antibody. This is not found persuasive. All references teach the hybridoma cell line that secretes the HPC-4 antibody, thus enabling the HPC-4 antibody.

The applicant argues that the Morrison and Queen references do not provide "the enablement to clone HPC4, nor provide any basis for believing that such a unique antibody could be cloned and still behave in its usual calcium dependant manner. This is not found persuasive. All antibodies, whether murine or human, share a high degree of structural homology, in the constant regions and the framework regions of the variable regions. Unique binding specificities are imparted to the antibody by the amino acid sequences of the hypervariable regions. One of skill in the art would reasonably expect the hypervariable regions of the HPC-4 antibody, when transplanted to a human antibody framework, would maintain the HPC-4 binding specificity. In support of this argument, the applicant makes reference to the "numerous declarations filed during the prosecution of the parent applications, even more strongly supporting the patentability of the claimed humanized or recombinant antibodies." Absent the submission of these declarations into the record of the instant case, these arguments can not be considered.

The applicant argues that the claimed antibody can not be made without being in possession of the nucleotide sequence of the heavy and light chain variable regions. While this is correct, the examiner does not agree with the argument that said nucleotide sequences are not obvious in view of the combined teachings of the references. The applicant argues that it is the examiner's position that the nucleotide sequence is obvious from the HPC-4 antibody protein itself. This is incorrect. The nucleotide sequence is obvious in view of teachings of the hybridoma cell line that secretes the HPC-4 antibody protein. Combining this hybridoma cell line with the methodologies for cloning and sequencing immunoglobulin variable region sequences taught in the Queen and Morrison references, the nucleotide sequence of the HPC-4 heavy and light chain variable regions (and thus, the amino acid sequences of the heavy and light chain) is obvious to one of skill in the art. The level of skill in the art of the cloning the genes encoding

antibodies was very high at the time of filing of the instant application, the applicant admits as much. The combined teachings make the nucleotide sequence obvious and make the claimed antibodies and methods obvious.

The applicant argues that the specificity of the HPC-4 antibody is highly unusual, requiring the presence of two distinct molecules: calcium and a peptide epitope, and that "one skilled in the art simply could not have any basis for determining whether or not an antibody with the unique specificity of the HPC-4 antibody could be cloned and this specificity expressed in a recombinant molecule. This is not found persuasive. While the HPC4 antibody may demonstrate a unique binding specificity, imparted by the unique amino acid sequence of its hypervariable regions, there is absolutely no evidence of record to indicate that the overall structure of the HPC4 antibody differs in any fashion from that of all antibodies in general and that such a variation from well known immunoglobulin structure plays a role in the unique binding specificity of the HPC4 antibody. All antibodies, whether murine or human, share a high degree of structural homology, in the constant regions and the framework regions of the variable regions. Unique binding specificities are imparted to the antibody by the amino acid sequences of the hypervariable regions. One of skill in the art would reasonably expect the hypervariable regions of the HPC-4 antibody, when transplanted to a human antibody framework, would maintain the HPC-4 binding specificity.

10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Nancy Johnson whose telephone number is (703) 305-5860. The examiner can normally be reached on Monday through Friday from 8:30 am to 6:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Nancy Johnson, can be reached on (703) 308-4310. Papers related to this application may be submitted to Group 1800 by facsimile transmission. Papers should be faxed to Group 1800 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 305-3014 or (703)

308-4242. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

11. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Nancy A Johnson
Primary Examiner

March 24, 1999